

**COMPLETE LIST OF CLAIMS AS CURRENTLY AMENDED SHOWING THE STATUS
OF EVERY CLAIM**

I claim:

1. (amended once) A method for selecting a drug candidate agent or composition of more than one drug candidate agent of possible clinical value in the treatment of a neurological disease selected from the group consisting of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, spinal muscular atrophy, Friedreich's ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome comprising
 - a. establishing, from a patient having a predetermined neurological disease, a cell culture of fibroblast cells;
 - b. establishing, from a person not having the predetermined neurological disease, a control cell culture of fibroblast cells;
 - c. subsequent concomitant cell culture growth of (1) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease; (2) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease; (3) a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease grown in the presence of an agent being investigated; (4) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of an agent being investigated; (5) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of a chemical stress protein-inducing parameter; and (6) a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of the stress protein-inducing parameter and the agent being investigated; and
 - d. use of an indicator system capable of detecting stress protein expression in said cultured fibroblast cells to identify as a drug candidate of possible clinical value that agent which does not prevent chemically induced stress protein expression in the control cell culture as per step c(6) but which does prevent stress protein expression in the patient cell culture as per step c(3).
2. (Original) The method according to claim 1 wherein the indicator system is
 - a. primary antibodies specific for stress proteins indicative of oxidative stress used in combination with secondary anti-immunoglobulin antibody-indicator conjugates,
 - b. specific antibody-indicator conjugates specific for stress proteins indicative of oxidative stress,
 - c. radiolabeled antibodies specific for stress proteins, or

d. resolution of stress proteins indicative of oxidative stress according to molecular weight and/or molecular charge.

3. (Original) The method of claim 2 wherein the antibody-indicator conjugates of step (a) or step (b) include biotin, fluorochrome or enzyme indicator functional groups.

4. (Original) The method of claim 2 wherein in step (d) the resolution is effected by means of gel electrophoresis.

5. (Original) The method of claim 1 wherein the drug candidate is selected by means of an indicator system capable of detecting the presence of a disease-related modified protein that is not the product of a defective disease-inducing gene responsible for the primary etiological event, and is not a stress protein, but is a protein containing a structural modification indicative of oxidative stress.

6. (Original) The method of claim 5 wherein the indicator system comprises

a. primary antibodies specific for the disease-related modified protein used in combination with secondary anti-immunoglobulin antibody-indicator conjugates,

b. specific antibody-indicator conjugates specific for the disease-related modified protein,

c. radiolabeled antibodies specific for the disease-related modified protein,

d. resolution of the disease-related modified protein by molecular weight and/or molecular charge.

7. (Original) The method of claim 6 wherein the secondary antibody-indicator conjugates of step (a) or step (b) contain biotin, fluorochrome or enzyme indicator functional groups.

8. (Original) The method of claim 6 wherein in step (d) the resolution is effected by means of gel electrophoresis.

9. (Original) A tissue culture system for selecting a drug candidate agent or composition of more than one drug candidate agent of possible clinical value in the treatment of a neurological disease comprising a plurality of tissue culture receptacles adapted for concomitant growth of

a. a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease,

b. a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease,

c. a cell culture of fibroblast cells originally obtained from the patient having a predetermined neurological disease grown in the presence of an agent being investigated,

d. a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of an agent being investigated,

e. a control cell culture of fibroblast cells originally obtained from a person not having the predetermined

neurological disease grown in the presence of a chemical stress protein-inducing parameter, and

f. a control cell culture of fibroblast cells originally obtained from a person not having the predetermined neurological disease grown in the presence of the stress protein-inducing parameter and the agent being investigated;

said plurality of tissue culture receptacles being useful in combination with an indicator system capable of detecting stress protein expression in said cultured fibroblast cells.

10. (Original) A tissue culture system according to claim 9 wherein the indicator system is capable of detecting expression of a disease-related modified protein which is not the product of a defective disease-inducing gene responsible for the primary etiological event, and is not a stress protein, but is a protein containing a structural modification indicative of oxidative stress.

11. (Original) A method of determining the presence of a predetermined neurodegenerative disease comprising the expression in cultured fibroblasts, obtained from a patient suspected of having the predetermined neurodegenerative disease, of at least one protein which is not the product of a defective disease-inducing gene responsible for the primary etiological event, that is, not a translation product of a defective gene responsible for the primary etiological event, but which is a disease-related stress protein and/or other protein modification indicative of oxidative stress or one or more other disease-related proteins.

12. (Original) The method of claim 11 for determining the presence of a neurodegenerative disease wherein the protein modification indicative of oxidative stress is a pathologically crosslinked protein present in cultured fibroblasts obtained from the patient.

13. (Original) The method of claim 12 wherein the one or more pathologically crosslinked protein is characterized in that it is of larger size than any control fibroblast strain protein normally and consistently seen under comparable tissue culture conditions.

14. (Original) The method of claim 11 used in combination with an indicator system so as to constitute a disease diagnostic test.

15. (Original) The method of claim 11 for the analysis of patient-derived cultured fibroblast samples wherein the indicator system is selected from hybridoma-derived primary antibodies specific for cultured fibroblast proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress to be used in combination with secondary anti-immunoglobulin conjugates which include biotin, fluorochrome or enzyme indicator functional groups, so as to provide an indicator capable of binding to the primary antibodies which, in turn, is

suitable for measurement by photometric or fluorometric assay procedures.

16. (Original) The method of claim 11 for the analysis of patient-derived cultured fibroblast samples wherein the indicator system is selected from hybridoma-derived specific antibody-indicator conjugates specific for cultured fibroblast proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress, said antibody-indicator conjugates including biotin, fluorochrome or enzyme indicator functional groups, so as to provide an indicator capable of binding to the primary antibodies which, in turn, is suitable for measurement by photometric or fluorometric assay procedures.

17. (Original) The method of claim 11 for the analysis of patient-derived cultured fibroblast samples wherein the indicator system is a radiolabeled hybridoma-derived antibody specific for cultured fibroblast proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress, so as to provide a basis for a disease diagnostic test by use of radioisotope measurement.

18. (Original) The method of claim 11 for the screening histologic samples obtained from patients having a neurodegenerative disease wherein the indicator system is a hybridoma-derived primary antibody specific for cultured fibroblast proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress to be used in combination with secondary anti-immunoglobulin antibody-indicator conjugates which include biotin, fluorochrome or enzyme indicator functional groups, so as to provide an indicator capable of binding to the primary antibodies which, in turn, is suitable for measurement by photometric or fluorometric assay procedures.

19. (Original) The method of claim 18 in which the histologic sample consists of a section of various body organ systems, blood or urine.

20. (Original) The method of claim 11 for the screening histologic samples of various bodily tissues obtained from a patient having a neurodegenerative disease wherein the indicator system is selected from hybridoma-derived specific antibody-indicator conjugates specific for cultured fibroblast proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress, said antibody-indicator conjugates including biotin, fluorochrome or enzyme indicator functional groups, so as to provide an indicator

capable of binding to the primary antibodies which, in turn, is suitable for measurement by photometric or fluorometric assay procedures.

21. (Original) The method of claim 20 in which the histologic sample consists of a section of various body organ systems, blood or urine.

22. (Original) The method of claim 11 wherein one or more cultured fibroblast-derived disease-related proteins which are stress proteins and/or other protein modifications indicative of oxidative stress are used as antigens in an ELISA assay system useful for diagnostic screening of patient blood or urine samples for the presence of disease-specific or disease-related auto-antibodies.

23. (Original) The method of claim 11 wherein the disease is a genetic neurodegenerative disease selected from the group consisting of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, familial forms of spinal muscular atrophy, Friedreich's ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy and Down's syndrome, including various individual genetic subvarieties thereof.

24. (Original) The method of claim 11 wherein the neurodegenerative disease is not known with certainty to be genetic origin, but the patient representing said disease has presented with clinical symptomology analogous to that of Charcot-Marie-Tooth disease, familial Alzheimer's disease, familial Parkinson's disease, Huntington's disease, familial forms of spinal muscular atrophy, Friedreich's ataxia, giant axon neuropathy, juvenile ceroid-lipofuscinosis, familial motor neuron diseases, juvenile diabetic polyneuropathy or Down's syndrome, including various individual genetic subvarieties thereof.

25. (Original) The method of claim 11 wherein the cultured fibroblasts have been genetically engineered by use of one or more constructed genetic vector so as to provide a molecular genetic model of a neurodegenerative disease.

26. (Original) A method useful for experimental screening of candidate drug agents consisting of mammalian fibroblasts obtained from a donor having a neurodegenerative disorder, said fibroblasts having been maintained in an in vitro tissue culture environment under circumstances such that they express one or more disease-related proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and are stress proteins and/or other protein modifications indicative of oxidative stress, the suppression of said expression of disease-related proteins which are not the translation product of a defective disease-inducing gene responsible for the primary etiological event and are stress proteins and/or other protein modifications indicative of oxidative stress in the presence of a beneficial therapeutic drug agent being a useful indicator of the candidate drug agent's potential clinical value, said suppression being measured by use

of indicator systems selected from the group consisting of but not limited to (a) primary antibodies specific for proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress to be used in combination with secondary anti-immunoglobulin antibody-indicator conjugates which include biotin, fluorochrome or enzyme indicator functional groups, (b) specific antibody-indicator conjugates specific for proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress, said antibody-indicator conjugates including biotin, fluorochrome or enzyme indicator functional groups, (c) radiolabeled antibodies specific for proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress and (d) resolution of proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress according to molecular charge by use of isoelectric focusing gel electrophoresis of said proteins and/or resolution of said proteins according to molecular weight by use of gel electrophoresis, followed by visualization of resolved protein spots on said electrophoresis gel and analysis of the electrophoretic pattern of the resolved cultured fibroblast proteins by visual examination or optionally by use of computer-assisted image processing technology, including reference to protein standards of known molecular weight and known isoelectric point.

27. (Original) A composition useful for experimental screening of candidate drug agents consisting of mammalian fibroblasts obtained from a donor having a neurodegenerative disorder, said fibroblasts having been maintained in an in vitro tissue culture environment under circumstances such that they express one or more disease-related proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and are stress proteins and/or other protein modifications indicative of oxidative stress, the suppression of said expression of disease-related proteins which are not the translation product of a defective disease-inducing gene responsible for the primary etiological event and are stress proteins and/or other protein modifications indicative of oxidative stress in the presence of a beneficial therapeutic drug agent being a useful indicator of the candidate drug agent's potential clinical value, said suppression being measured by use of indicator systems selected from the group consisting of but not limited to (a) primary antibodies specific for proteins which are not the product of a defective disease-inducing gene

responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress to be used in combination with secondary anti-immunoglobulin conjugates which include biotin, fluorochrome or enzyme indicator functional groups, (b) specific antibody-indicator conjugates specific for proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress, said antibody-indicator conjugates including biotin, fluorochrome or enzyme indicator functional groups, (c) radiolabeled antibodies specific for proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress and (d) resolution of proteins which are not the product of a defective disease-inducing gene responsible for the primary etiological event and which are stress proteins and/or one or more other protein modifications indicative of oxidative stress according to molecular charge by use of isoelectric focusing gel electrophoresis of said proteins and/or resolution of said proteins according to molecular weight by use of sodium dodecyl sulfate gel electrophoresis, followed by visualization of resolved protein spots on said electrophoresis gel and analysis of the electrophoretic pattern of the resolved cultured fibroblast proteins by visual examination or use of computer-assisted image processing technology, including reference to protein standards of known molecular weight and known isoelectric point.